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SYNTHESIS, THERMAL TRANSFORMATIONS, AND MASS SPECTROMETRIC FRAGMENTATION OF 4,4'-[1,2-BIS(5-HYDROXY-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL)ETHANE-1,2-DIYL]-BIS(5-METHYL-2-PHENYL-1,2-DIHYDRO-3*H*-PYRAZOL-3-ONE)

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Quinoxaline reacted with 3-methyl-1-phenylpyrazol-5-one at room temperature in the presence of triethylamine in DMSO solution, to form 4,4'-[1,2-bis(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-ethane-1,2-diyl]bis(5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one). Heating of the obtained crystalline product at 240-250°C temperature led to the known 4-[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one. The mass spectral fragmentation of the obtained compounds was characterized.

Keywords: 3-methyl-1-phenylpyrazol-5-one, quinoxaline, tetrapyrazolylethane, thermogravimetry.

It is known that quaternary *N*-alkyl salts of quinoxaline react with 1,3-diketones, forming double addition or cycloaddition products at the C(2)–C(3) bond [1, 2]. We have found that unsubstituted quinoxaline reacted with 1,3-dimethylbarbituric acid at room temperature to form monosubstituted product in the absence of external acid-base catalysis, and we described a reaction of quinoxaline with ethyl 3-[(1,3-dimethyl-2,6-dioxotetrahydropyrimidin-4(1*H*)-ylidene)hydrazono]butanoate on heating in an acidic medium with the formation of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione [3].

We recently published a preliminary report on an unusual reaction of quinoxaline (**1**) with 3-methyl-1-phenylpyrazol-5-one (**2**) in the presence of triethylamine [4], forming 4,4'-[1,2-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethane-1,2-diyl]bis(5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) (**3**) in 47% yield and the known 4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylidene]-5-methyl-2-phenyl-2,4-di-hydro-3*H*-pyrazol-3-one (**4**) [5] in 7% yield (Scheme 1). In addition, *o*-phenylenediamine (**5**) was also isolated from the reaction mixture.

The mechanism of the tetrapyrazolylethane **3** formation apparently included the following stages: nucleophilic addition of two 3-methyl-1-phenylpyrazol-5-one (**2**) molecules at the C=N bonds of quinoxaline

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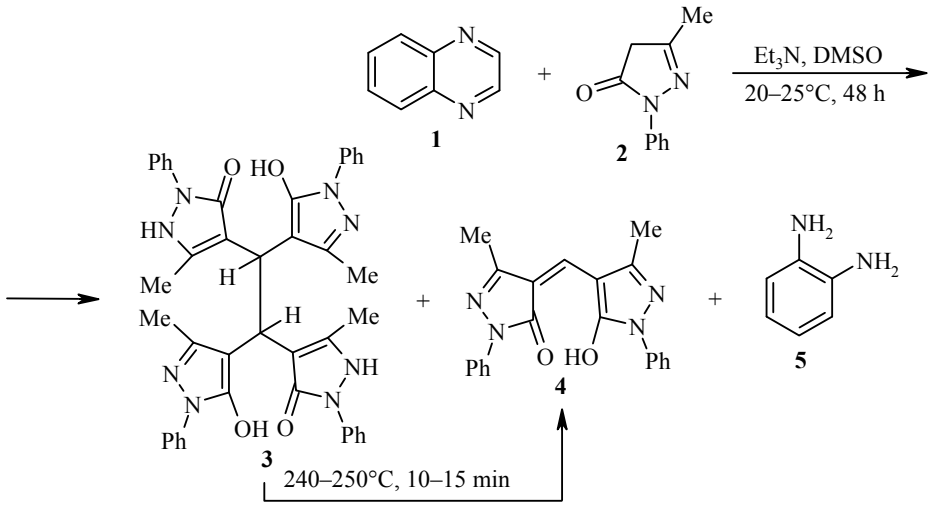
(**1**) with the formation of 2,3-bispyrazolyl adduct, elimination of *o*-phenylenediamine, and a second addition of two molecules of pyrazolone **2** to the dipyrazolylethane intermediate [4].

We established the precise structure of the tetrapyrazolylethane **3** by X-ray structural analysis [4].

Scheme 1

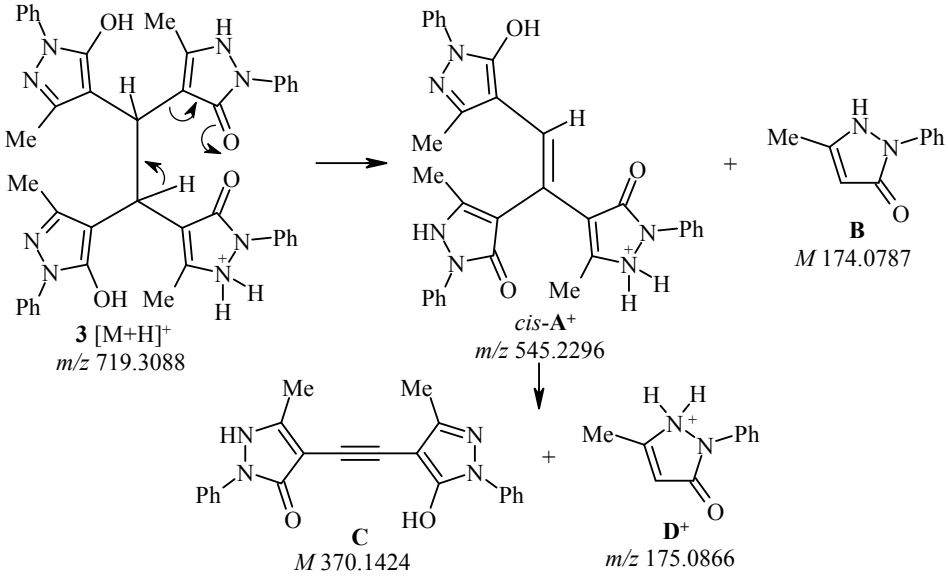


Molecular ions of compound **3** upon collision with argon in a CID cell (collision cell) in MS_2 mode (tandem mode) at 25 eV ion energy gave a mass spectrum that, apart from the molecular ion, also contained ion peaks with *m*/*z* 545.2201, 371.1460, 360.1575 (doubly charged ion), and 175.0840. The formation of ions with *m*/*z* 545.2201, 371.1460, and 175.0840 was explained by consecutive loss of two pyrazolone fragments from two different dipyrazolylmethane fragments of the molecular ion with *m*/*z* 719.3088 $[M+H]^+$. This fragmentation of the molecular ion may be rationalized by rearrangement involving a hydrogen atom in the eliminated pyrazolone fragment.

A similar fragmentation involving hydrogen atom transfer occurs in the McLafferty rearrangement [6].

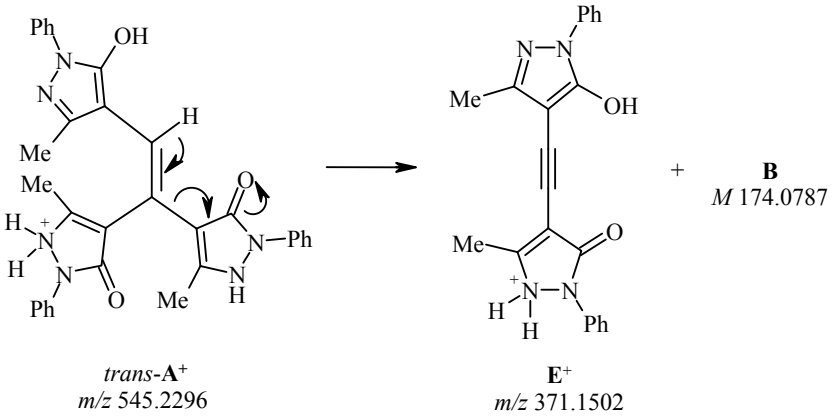
Indeed, it may appear that for the *cis* isomer $\mathbf{A}^+$ with *m*/*z* 545.2296, decomposition produced the ion $\mathbf{D}^+$ with *m*/*z* 175.0866, and the neutral molecule **C** with calculated mass of 370.1424 was formed by its decomposition (Scheme 2).

Scheme 2



As the result of an analogous decomposition of isomer *trans*-$\mathbf{A}^+$, the ion $\mathbf{E}^+$ with *m*/*z* 371.1502 and the neutral pyrazolone **B** with relative molecular mass of 174.0787 were formed (Scheme 3).

Scheme 3

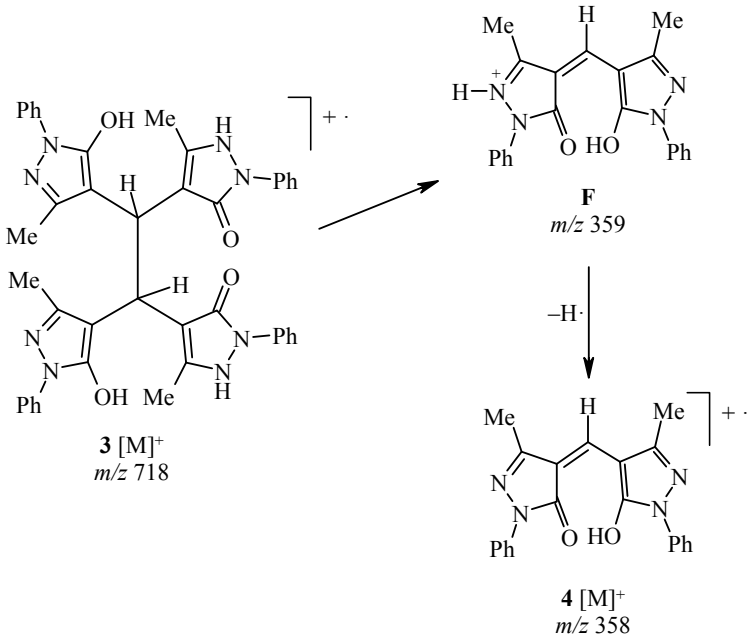


trans-$\mathbf{A}^+$
m/z 545.2296

$\mathbf{E}^+$
m/z 371.1502

In the electron impact (EI) mass spectrum at 200-240°C, the molecular ion of tetrapyrazolylethane **3** was not observed, but a strong ion signal with *m*/*z* 358 (30%) was observed in addition to a weak signal at *m*/*z* 370 (11%). The registration of such ions in the mass spectrum suggests the presence of two routes for molecular ion fragmentation: homolytic cleavage of the C–C bond into two dipyrazolylmethane fragments with subsequent loss of a hydrogen radical from the unstable fragment **F** (Scheme 4), or elimination of two

Scheme 4



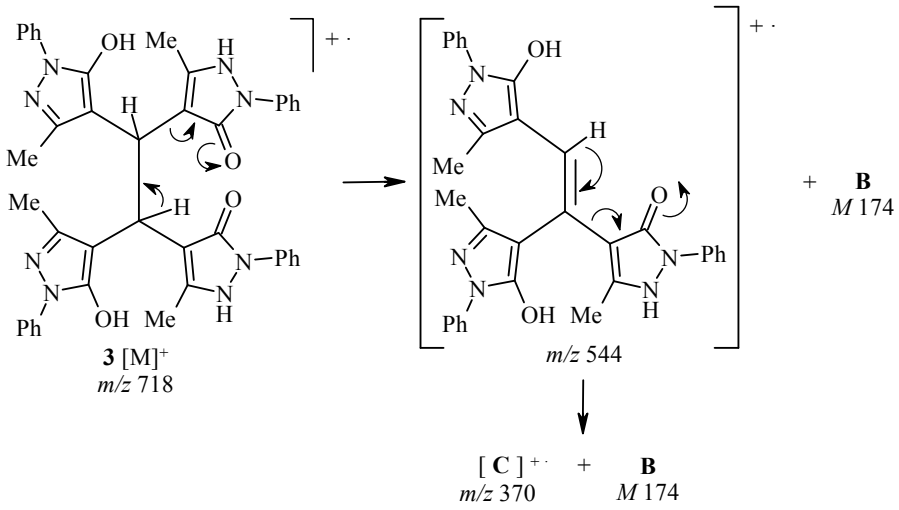
3 $[M]^+$
m/z 718

4 $[M]^+$
m/z 358

molecules of pyrazolone (fragment **B**) from different dipyrazolylmethane fragments concurrently with hydrogen rearrangement of the molecular ion leading to the dipyrazolylethyne **C** ion with *m*/*z* 370 (Scheme 5).

It was previously shown that the tetrapyrazolylethane **3** was converted into the dipyrazolylmethane **4** in 48-50% yield by brief heating at reflux in DMF or in the presence of iodine even at room temperature. In a continued investigation of the tetrapyrazolylethane **3** properties it was also found that the dipyrazolylmethane **4** was formed in 50% yield when crystals of compound **3** were heated to 240°C.

Scheme 5



It was found in a thermogravimetric study (curves TT and DTT, Fig.1) that two moles of crystal hydrate water were lost from a sample of compound **3** in the 50-130°C temperature range over 2-10 min, which was confirmed by IR spectrum of the vapor. At the same time, a weak exothermic effect (DTA curve) was observed at a temperature of about 200°C. Such an effect is possibly connected to homolytic cleavage of a C–C bond, eIimination of hydrogen, and formation of dipyrazolylmethane **4** (this same process was evidently observed upon EI ionization in the mass spectrometer, Scheme 4). Apparently, simultaneously with the cleavage of the ethane bond two pyrazolone fragments were eliminated from different dipyrazolylmethyl moieties of compound **3**. Thus, the dipyrazolylethyne derivative **C** (*m*/*z*=370) was formed, which was confirmed by the presence of the corresponding ion signals in the EI mass spectrum (Scheme 5). The evolution of 3-methyl-1-phenylpyrazolyl-5-one (**2**) was confirmed by IR spectra of the gas phase. The intensity of pyrazolone evolution was estimated by

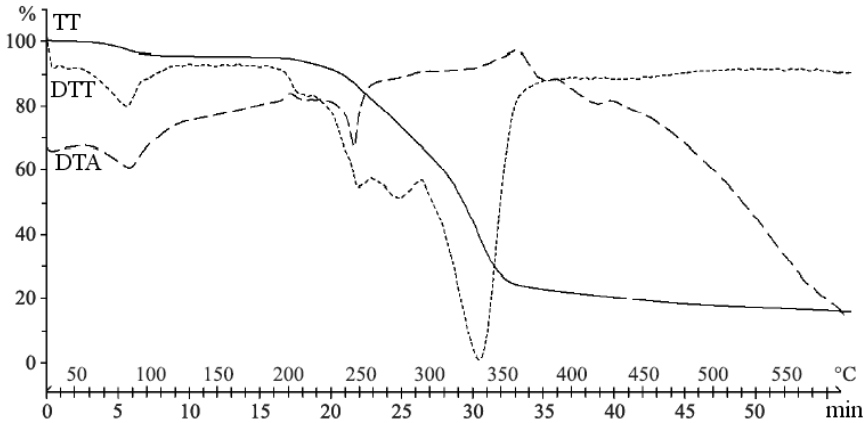


Fig. 1. Thermogram of compound **3** (TT – curve of weight loss, DTT – differential curve of weight loss, DTA – differential curve of the thermal effects).

the integrated area of a characteristic absorption band (1781-1717 cm^{-1}), indicating an evolution of this reaction product in two stages with maxima at 290 and 340°C. The evolution of pyrazolone fragments likely occurs from the tetrapyrazolyl derivative and also on decomposition of the dipyrazolylmethane intermediate **4** (*m*/*z* 358).

The obtained data suggest that apparently the main direction of 4,4'-[1,2-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethane-1,2-diyl]bis(5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) thermolysis was homolytic cleavage at the ethane C–C bond. It should also be noted that the ions observed in mass spectra under mild ionization conditions (electrospray) could be explained by pyrazolone elimination from different dipyrazolylmethane units of the initial tetrapyrazolylethane. Protonated dipyrazolylethyne derivatives (*m*/*z* 371) were thus formed by mass spectral fragmentation. Another direction of tetrapyrazolylethane cleavage producing dipyrazolylethyne was indicated by the presence of ions with *m*/*z* 370. However, preparative synthesis of these derivatives has not yet been achieved.

EXPERIMENTAL

IR spectra of the evolved vapors and gases were recorded with a Nicolet iS10 instrument with TFA/FT-IR attachment (Thermo Scientific). The IR spectra of water vapor and 3-methyl-1-phenylpyrazol-5-one acquired during analysis were compared with data from NIST Standard Reference Database 69: NIST Chemistry WebBook [http://webbook.nist.gov/chemistry]. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer in DMSO-d_6 with residual solvent signals as internal standard (2.49 ppm). High-resolution mass spectra were recorded with a Bruker Daltonics micrOTOF-Q II instrument equipped with an electrospray ionization source, a six-port valve and a KD Scientific direct sampling device (flow rate 180 μl/h). The nominal resolution of the instrument was 17500. Positively charged ions were recorded within the *m*/*z* range of 50-900 Da. External graduation of the apparatus at 6 points was performed for each series of experiments. Reference peaks of lithium formate clusters were obtained by injection into the apparatus of 10 mmol/l LiOH solution in a 1:1 mixture of 2-PrOH with 0.2% aqueous HCOOH. EI mass spectra (70 eV) were recorded with a Varian MAT-311 apparatus. Thermogravimetric analysis of the compound **3** dihydrate was performed with a Mettler Toledo TGA/DSC 1 instrument at a 10°C/min heating rate under an argon stream (60 ml/min).

Reaction of quinoxaline (1) with 3-methyl-1-phenylpyrazol-5-one (2) was performed according to a modification of a described method [4]. A solution of quinoxaline (**1**) (0.130 g, 1.0 mmol), 3-methyl-1-phenyl-pyrazol-5-one (**2**) (0.684 g, 4.0 mmol), and Et_3N (0.3 ml) in DMSO (2 ml) was maintained at room temperature for 48 h. The reaction mixture was diluted with water (1:1) and acidified to pH 5-6 with 15% aqueous HCl. The precipitate was filtered off and washed with hot EtOH (10 ml) to give dihydrate of **4,4'-[1,2-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethane-1,2-diyl]bis(5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) (3).** Yield 0.445 g (59%), colorless crystalline powder, mp >250°C (mp >250°C [4]). The filtrate was cooled, and the precipitate of **4-[(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylidene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4)** was isolated. Yield 0.025 g (7%), orange crystals, mp 180-182°C (mp 181-182°C [5]). The filtrate was neutralized to pH 7-8 and extracted with $CHCl_3$. The extract was evaporated in vacuum. *o*-Phenylenediamine (**5**) (R_f 0.33) was isolated from the solid residue by preparative TLC on silica gel with $CHCl_3$–EtOH (9:1) as eluent. Yield 0.025 g (23%). The ^{1}H NMR spectra of compounds **3** and **4** were identical to those described in papers [4, 5], respectively.

Compound 3. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 370 (11), 358 (30), 174 (34), 91 (55), 77 (100). Found, %: C 67.18; H 5.32; N 15.19. $C_{42}H_{38}N_8O_4 \cdot 2H_2O$. Calculated, %: C 66.83; H 5.61; N 14.84.

Compound 4. A. Compound **3** (0.020 g, 0.03 mmol) was heated at 240-250°C for 10-15 min. The solid residue was cooled and treated with EtOH (1.5-2.0 ml). The precipitate was filtered off. Yield 0.010 g (50%). The melting point and spectral characteristics of the obtained compound **4** corresponded to those for a sample obtained by the methods described above.

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